Structural and Functional Brain Anatomy in Children with Developmental Dyscalculia: What Counts?

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„Etwas zu sehen,
was allgegenwärtig ist,
aber unserer Erkenntnis bisher verborgen."

o.V.

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SUMMARY

Calculation ability represents an extremely complex cognitive process. It has been understood to be associated with and depend upon multifactor abilities, including verbal, spatial, memory, and executive functions (Ardila et al., 1998).

The complexity of numerical processing may refer to the difficulties investigating its disorder: Developmental Dyscalculia (DD). The underlying deficits, which cause DD, remain unanswered but various factors have been proposed. These can be classified into two models: Domain general or domain specific factors. An involvement of domain specificity in the development of DD results from infant and non-human primate studies (McCrink and Wynn, 2004; Nieder, 2005). It has been argued that the core aspect of numerical cognition is an innate "number sense", which is a short-hand term for our ability to quickly understand, approximate and manipulate numerical quantities (Dehaene, 1997). The core deficit hypothesis proposes that an impaired system leads to deficits in number sense what is the cause of a least some types of DD. This 'number sense' is located in the parietal lobe and therefore, children with DD should exhibit a dysfunction of this region.

On the other hand, domain general factors, as attention or working memory, which stand for an involvement of the executive system in calculation, are not in the focus of investigations about the underlying deficits of DD.

The main goal of this thesis was to evaluate the neural network of children with DD in respect of a domain general approach.

In Study A, entitled "Optimized Voxel Based Morphometry in Children with Developmental Dyscalculia" we investigated dyscalculic children compared to control children by use of voxel-based morphometry. This method reveals anatomical differences between groups and is independent of cognitive functions. Results show decreased grey matter volume in the right IPS. If it is assumed that the right IPS exclusively serves as a region that represents a core analog representation of number this finding would contribute to the domain specific hypotheses, described above. But there were additional clusters at the bilateral middle frontal gyrus, the left inferior

frontal gyrus and bilateral anterior cingulum which refer to possible domain general impairments of the attentional and the working memory system, which might have a negative effect on the acquisition of number representation and number processing capacities.

In Study B, entitled “Dysfunctional Neural Network of Spatial Working Memory Contributes to Developmental Dyscalculia” special interest has been addressed to neural functions of a domain general factor, spatial working memory. Functional magnetic resonance imaging (fMRI) was used to examine children with and without DD with a spatial working memory paradigm. We found reduced activation in working memory relevant brain areas, such as the right IPS, the right inferior frontal lobe and in the right insula in children with DD when compared to control group. Decreased activation in the right IPS of children with DD during a spatial working memory task may indicate that more domain general factors such as working memory influence the acquisition of arithmetic competencies and the development of a mental number line. Therefore, our data support the general domain hypothesis and we conclude, that poor spatial working memory capacity in DD influences the formation of a core understanding of numerical information and the development of a ‘mental number line’.

ZUSAMMENFASSUNG

Das Rechnen stellt einen hochkomplexen kognitiven Prozess dar, welcher verschiedene multifaktorielle Fähigkeiten wie verbale, räumliche, Gedächtnis- und Exekutivfunktionen in sich vereint (Ardila et al., 1998). Die Komplexität der Zahlenverarbeitung spiegelt sich auch in der Erforschung der Störung der Zahlenverarbeitung, der sogenannten Dyskalkulie wider. Sind doch die zugrunde liegenden Defizite, welche zu einer Dyskalkulie führen bis anhin unbekannt. Die verschiedenen Ansätze, welche diskutiert werden, lassen sich in zwei Gruppen klassifizieren: In domänen-übergreifende und domänen-spezifische Faktoren. Als domänen-übergreifend werden Fähigkeiten wie beispielsweise Gedächtnis- und Exekutivfunktionen bezeichnet. Dem gegenüber stehen domänen-spezifische Faktoren, welche direkt mit der eigentlichen Fähigkeit in Verbindung gebracht werden können. Den Einfluss eindimensionaler Faktoren auf die Entwicklung einer Dyskalkulie liefern Primatenstudien sowie Studien mit Kleinkindern (McCrink and Wynn, 2004; Nieder, 2005). Es wird angenommen, dass die Kernkompetenz der Zahlenverarbeitung durch einen angeborenen Zahlensinn repräsentiert wird, welcher es uns ermöglicht, Zahlen schnell zu erfassen, abzuschätzen und mit Mengen umzugehen (Dehaene, 1997). Die daraus entstandene Kern-Defizit-Hypothese beschreibt eine Beeinträchtigung dieses Systems als hauptverantwortlich für die Schwierigkeiten im Umgang mit Zahlen und der Entwicklung mindestens einiger Formen der Dyskalkulie. Dieser Zahlensinn wird im Parietallappen lokalisiert. Eine Dysfunktion dieser Region wird als ursprünglich für die Entwicklung einer Dyskalkulie angenommen.

Demgegenüber stehen domänen-übergreifende Einflussfaktoren, wie Aufmerksamkeit oder Arbeitsgedächtnis, welche den Bereich der exekutiven Funktionen in die Entwicklung der Rechenfähigkeiten mit einschliessen.

Das Hauptziel dieser Arbeit bestand darin, die neuronalen Netzwerke von Kindern mit Dyskalkulie in Bezug auf einen domänen-übergreifenden Ansatz hin zu untersuchen. In Studie A, welche den Titel "Optimized Voxel Based Morphometry in Children with Developmental Dyscalculia" trägt, wurde mit Hilfe der voxel-basierten Morphometrie

(VBM) die Gehirne von Kindern mit Dyskalkulie mit denen von normal-rechnenden Kindern verglichen. Die Methode der voxel-basierten Morphometrie zeigt unabhängig von kognitiven Funktionen die anatomischen Unterschiede zwischen Gruppen auf. Die resultierenden Unterschiede verweisen auf ein vermindertes Volumen an grauer Substanz im rechten intraparietalen Sulcus (IPS) bei Dyskalkulikern. Würde der rechte IPS als exklusive Region dienen, welche als analoge Zahlenrepräsentation betrachtet werden kann, dann würde dieser Volumenunterschied im rechten IPS die oben beschriebene domänen-spezifische Hypothese unterstützen. Jedoch verweisen die zusätzlichen Unterschiede in den bilateralen Gyri frontalis medii, im linken inferioren frontalen Gyrus und im bilateralen anterioren Cingulum auf mögliche domänen-übergreifende Beeinträchtigungen, wie Störungen im Bereich der Aufmerksamkeit und des Arbeitsgedächtnisses. Probleme in diesen Bereichen können somit einen negativen Effekt auf den Erwerb von Zahlenrepräsentationen und Zahlenfertigkeiten ausüben.
In Studie B mit dem Titel "Dysfunctional Neural Network of Spatial Working Memory Contributes to Developmental Dyscalculia" wurde der Einfluss des räumlichen Arbeitsgedächtnisses als ein domänen-übergreifender Faktor mittels funktioneller Magnetresonanztomographie (fMRT) näher untersucht. Dabei zeigten sich bei Kindern mit Dyskalkulie verminderte Aktivierungen im rechten IPS, dem rechten inferioren Frontallappen und in der rechten Insula. Da diese reduzierte Aktivierung im rechten IPS bei Kindern mit Dyskalkulie während einer räumlichen Arbeitsgedächtnisaufgabe für domänen-übergreifende Faktoren spricht, welche einen Einfluss auf den Erwerb von Zahlenfertigkeiten und die Entwicklung eines mentalen Zahlenstrahls ausüben, schliessen wir daraus, dass bei Kindern mit Dyskalkulie eine eingeschränkte räumliche Arbeitsgedächtnis-Kapazität die Bildung einer Kernkompetenz in Bezug auf Rechenfähigkeiten hemmt und somit die Entwicklung eines mentalen Zahlenstrahls negativ beeinflusst.

1. Introduction

Numbers are part of our every day life. We use them in the context of calculation and mathematics, but they play also a role in ordinary contexts such as remembering a telephone number, cooking with given quantities in recipes, or when buying something in a shop. Difficulties in learning to deal with quantities or losing these abilities as a result of a neurological disorder result in individual tragedies and social costs. Such problems deserve careful study and consideration by scientists and practitioners alike (Geary, 2000). There have been significant advances in understanding how the adult brain represents numerical quantities and enables the processing of mathematical problems, and there has been an increasing interest in developmental studies of number processing in children. In contrast, little research has focused on atypical neural representations of numbers, despite the fact that deficits in number processing and basic mathematical skills are as common as impairments of reading and writing (Ansari and Karmiloff-Smith, 2002; Shalev et al., 2000).

Developmental dyscalculia (DD) is defined, according to the International Classification of Diseases, 10th revision (ICD-10, F81.2, (WHO, 2005)), as a significant discrepancy between specific math performance and general intelligence that cannot be explained by mental retardation, inappropriate schooling or poor social environment.

The investigation of children with DD poses a special challenge, as the outcome of this disorder is very heterogeneous. A great variety of non-specific problems, including slow speed of processing, poor working memory span, problems of attention, and deficits in the long-term storage of arithmetic facts as well as anxiety have to be considered as important factors that may influence arithmetic performance (Temple and Sherwood, 2002).

Therefore, the goal of the present thesis is to evaluate the neural mechanisms underlying DD. Firstly, we investigated the anatomical neuronal substrate of this disorder and, second, we analyzed one of the possible functional brain processes contributing to DD, spatial working memory.

Now, before turning to the experimental part, the methods used in this thesis are briefly introduced: voxel-based morphometry and functional magnetic resonance imaging. This section is followed by a short overview about the development of numerical cognition and an introduction to the principle theme of this thesis, developmental dyscalculia. After the presentation of the experiments the general discussion summarizes the results.

2. Magnetic Resonance Imaging

This chapter gives a short introduction into the methods used in Experiment 1 and 2. The principles of voxel-based morphometry and functional magnetic resonance imaging are explained.

2.1 Voxel Based Morphometry

Voxel-based-morphometry (VBM) (Ashburner and Friston, 2000) is a whole-brain, unbiased technique for characterizing regional cerebral volume and tissue concentration differences in structural magnetic resonance images.

It involves a voxel-wise comparison of the local concentration of grey and white matter between two groups of subjects. The value of this method is that it allows for a comprehensive statistical comparison of neuroanatomical differences, not just in specific structures, but also throughout the entire brain. This is achieved by spatially normalising all the structural images to the same stereotactic space, segmenting the normalised images into grey and white matter, smoothing the grey and white matter images and finally performing a statistical analysis to localize significant differences between two or more experimental groups. The output is a statistical parametric map (SPM) revealing regions in which grey or white matter differ significantly among the groups.

This standard preprocessing protocol tends to result in misinterpretations of structural differences as a result of normalization, which are not directly related to grey or white matter volumes (Mechelli et al., 2005). A way of minimizing this potential source of error is to perform the normalisation using the segmented grey and white matter volumes rather than on the whole-brain images described by Good and colleagues (2001). If all the data entering into the statistical analysis are only derived from grey matter, then any significant differences must be due to grey matter. Likewise, if all the data entering into the statistical analysis are derived only from white matter, then any significant differences must be due to white matter changes. One reservation with this approach, however, would be that the segmentation has to be performed on images in native space. The Bayesian priors, however, encode a priori knowledge about the spatial distribution of different tissues in normal subject that are normalized in stereotactic space. A way of circumventing this problem is to use an iterative version of segmentation and normalisation operators. First, the original structural MRI images in native space are segmented. The resulting grey and white matter images are then spatially normalized to grey and white matter templates respectively to derive the optimized normalisation parameters. These parameters are then applied to the original, whole-brain structural images in native space prior to a new segmentation. This recursive procedure, also known as "optimized VBM", has the effect of reducing the misinterpretation of significant differences relative to "standard VBM". In our special case, investigating children, we used additionally a paediatric brain template derived from a large population of normal, healthy children (http://www.irc.cchmc.org /software/pebrain.php). Details of the analyses are described in Section 4.

2.2 Functional magnetic resonance imaging

In contrast to VBM, brain activation patterns demonstrated by functional magnetic resonance imaging (fMRI) are strongly task dependent. This method provides images of the brain function based on the hemodynamic response related to neural activity in the brain. Therefore, this method measures the neuronal activity indirectly with very high spatial resolution in the range of millimetres, but with low temporal resolution in the range of seconds. The time course of the fMRI hemodynamic response is roughly a low pass filtered version of the electric neuronal activity (Logothetis et al., 2001). It exploits the fact that oxygenated haemoglobin has different magnetic properties than deoxygenated haemoglobin. When a brain area is active more oxygenated blood is transported to that location, thus increasing both cerebral blood flow and blood volume. The oxygen supply has been shown to overcompensate the neuronal need (Fox and Raichle, 1986), thus resulting in an increase in the ratio between oxygenated and deoxygenated blood. Due to the different magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) haemoglobin an increase in the MR-signal, the so called “Blood-Oxygen-Level-Dependent” (BOLD) contrast arises. Systematic gradient variation ("switching") changes the frequency of this signal and is used to localize this BOLD contrast to about 1 mm to 1 cm. The fact that this effect is observed only after several seconds is mostly responsible for the poor time resolution (> 1 sec) of BOLD-fMRI. A further limitation of this method is its dependency on a comparison condition, which forms the baseline to define activation. Thus, activations are always relative to contrast, which can differ between individuals and more important between groups. Although the tight coupling between neuronal activity and oxygen consumption is widely accepted and partly proved (Logothetis et al., 2001; Logothetis and Wandell, 2004) the described differences are thought to make these methods rather complementary than redundant.

3. Development of Numerical Cognition

This section introduces to the developmental principles of number processing from childhood to adulthood and the neuronal representation of numerical information.

Meanwhile, there are significant advances in understanding how humans represent numerical quantities and enables the processing of mathematical problems. Infants of only a few months of age and non-human primates already share the ability to discriminate numerical magnitudes (Hauser et al., 2003; McCrink and Wynn, 2004), but one striking way in which humans differ from non-human primates is in their ability to represent numerical quantity using abstract symbols (e.g. Arabic numerals).

Von Aster (2005) proposed a 4-step developmental model, in which early preverbal core-system representation of cardinal magnitude (cardinality; step 1) provides the meaning of 'number', a precondition to acquire linguistic (step 2), and Arabic (step 3) number symbols, these abilities on the other hand allow intact counting skills. To construct and automatise the conception of a spatially organized ordinality of numbers (mental number line), children need to interlink the understanding of magnitude (core systems) with the symbolic and spatial-ordinal properties of number. This process requires, among others, an increase in working memory capacity, which enables neuroplastic development of an expanding mental number line during school years (step 4). (See Figure 1)

The early available preverbal abilities (step 1) have also been called the "core-systems of number" (Feigenson et al., 2004; Spelke, 2003). It has been argued that the core aspect of numerical cognition is a "number sense", which is a short-hand term for our ability to quickly understand, approximate and manipulate numerical quantities (Dehaene, 1997). This model proposes two innate core systems for representing number. One system represents number in an exact way but has a fixed upper limit; the other system has no size limit but represents number only approximately. Both systems are claimed to have a phylogenetic origin and constitute the basis for ontogenetic development. As such, each system's representational principles are reflected in human adult math performance: subitizing[1] is ascribed to the exact system whereas symbolic number processing is based on a mapping to the approximate system.

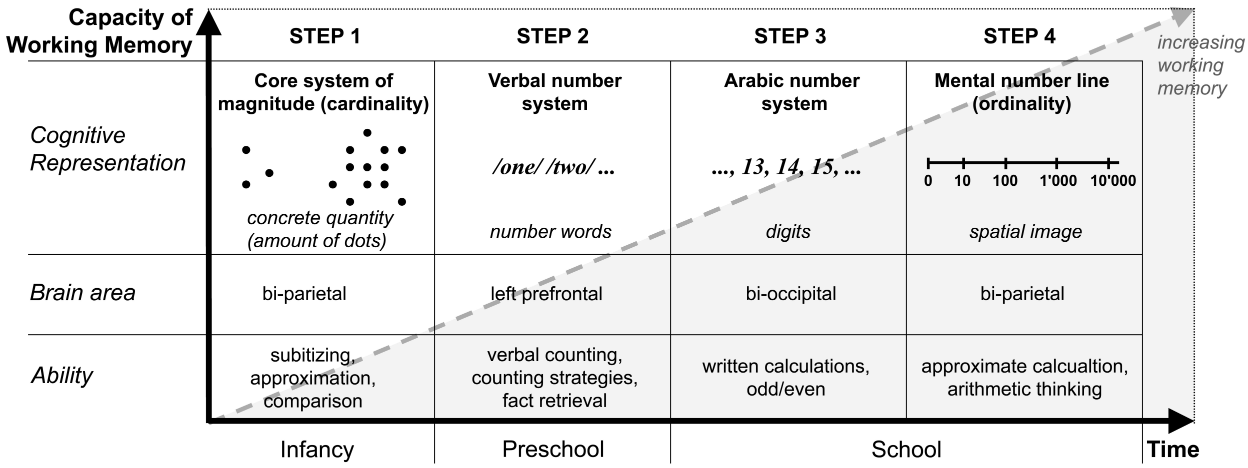

Figure 1: Four-step-developmental model of numerical cognition (von Aster, 2005).

These core-system abilities are not identical to what school-aged children and adults utilize when operating on a mental number line. Von Aster (2005) argues that the mental number line is a product of experience-dependent, neuroplastic development that requires more than just the availability of intact core-systems, and takes place during preschool and primary school years. Additionally, the role of visual imagery, language, and working memory functions is also important in the development of the mental number line.

There is now evidence that the mental number line of ordinal sequences is spatially coded. The association between numbers and space was first demonstrated by a response-side effect, the so called Spatial Numerical Association of Response Codes (SNARC) effect in number comparison, when subjects had to indicate whether a

[1] to perceive at a glance the number of items presented

number was smaller or larger than a reference number (Dehaene et al., 1993; Dehaene et al., 1990). Subjects answer faster for small numbers with their left hand and faster for large numbers with the right hand. This effect arises in 2nd and 3rd grade school children (Schweiter et al., 2005) and in a recent study (van Galen and Reitsma, 2008) a SNARC effect was also found from the age of 7 years onward but when number magnitude was irrelevant, a SNARC effect was found only in 9-year-olds and adults. These results are taken to suggest that 7-year-olds represent number magnitudes in a way similar to that of adults and that when perceiving Arabic numerals, children have developed automatic access to magnitude information by around 9 years of age.

3.1 Neural correlates of numerical development

The underlying brain processes of arithmetic performance in adults are well studied. Functional brain imaging (fMRI) studies with typically achieving adults have identified a number of brain regions involved in the performance of arithmetic tasks (Dehaene et al., 1999; Kawashima et al., 2004; Rivera et al., 2005; Rueckert et al., 1996). Dehaene and colleagues (2003) describe the horizontal segment of the intraparietal sulcus (HIPS) as the region most specifically involved in number representation. Activation of this region is observed in many different number processing tasks (Pinel et al., 2001), especially when nonverbal representation of numerical quantity, conceptualized as "mental number line", is required. Additionally, there is a network of areas activated during number processing which includes frontal and anterior cingulate components (Chochon et al., 1999), these areas are related to working memory and visuospatial attention (Corbetta et al., 1993; D'Esposito et al., 2000; Postle et al., 2000). Activation of the left angular gyrus and left prefrontal regions are mainly implicated in exact, verbal memory based, language-dependent calculation (Dehaene, 1992; Dehaene and Cohen, 1995; Dehaene et al., 1999).

FMRI studies of numerical processing in typically achieving children revealed similar functional networks compared to adults (Cantlon et al., 2006; Kawashima et al., 2004; Rivera et al., 2005). However, children primarily engaged frontal regions, suggesting that children require comparatively more working memory and/or allocation of attentional resources to complete a calculation task. Over development, an ontogenetic shift is assumed from frontal towards greater parietal engagement. This change may reflect maturation processes due to practice and more automatised problem solving strategies. Adults, on the other hand, showed an increased activation in parietal areas referring to a functional specialization for the processing of mental arithmetic and numerical magnitude (number line) over age (Ansari and Dhital, 2006; Ansari et al., 2005; Kucian et al., 2006; Rivera et al., 2005) (See Figure 2).

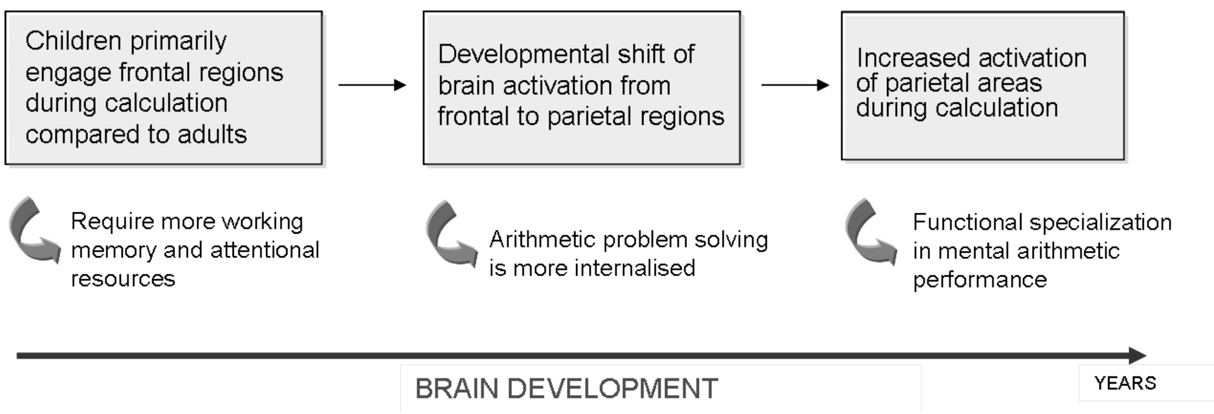

Figure 2: Developmental Model of Calculation (neural and behavioral)

4. Developmental Dyscalculia

In this chapter the term 'Developmental Dyscalculia' is introduced together with its prevalence and aetiology. Further, a discussion about domain specificity vs. domain generality in the field of numbers and a description of the neural correlates of DD is given.

4.1 Definition

The term *developmental dyscalculia* (DD) refers to a cognitive disorder of childhood, impairing the normal acquisition of arithmetical skills (American Psychiatric Association, 1987). According to the International Classification of Diseases, 10th revision (ICD-10, F81.2), DD is defined as a significant discrepancy between specific mathematical abilities and general intelligence that cannot be explained by mental retardation, inappropriate schooling or poor social environments (WHO, 2005).

In the DSM-IV (American Psychiatric Association, 1994) the term DD has been changed to Mathematics Disorder, however in the Neuropsychology literature the term DD lasts.

4.2 Prevalence and Epidemiology

Prevalence studies on DD have been carried out in various countries using different definitions (Klauer, 1992; Kosc, 1974). Despite the lack of consistent definitions, the prevalence of DD across countries is relatively uniform, ranging from 3 to 6 % in the normal population (Shalev et al., 2000). Therefore, DD is not a rare learning disability and the prevalence is similar to that of developmental dyslexia and attention deficit hyperactivity disorder (ADHD).

Unlike other learning disabilities for which there is generally a predisposition of boys relative to girls, the majority of the studies on DD have shown that both sexes are equally affected (Klauer, 1992; Shalev et al., 2000).

4.3 Aetiology

To date no consensus about the aetiology of DD has been reached. Possible contributing factors such as genetic predisposition, neurologic abnormalities, and environmental deprivation have been proposed. Other researchers implicate further such as poor teaching, low intelligence, and mathematical anxiety (Ashcraft, 1995). The heterogeneity of DD and the frequent association with dyslexia and/or attention disorders constitutes another influencing factor in aetiology.

Additionally, a great variety of non-specific problems, including slow speed of processing, poor working memory span, attentional disorders, and deficits in the long-term retrieval of arithmetic facts have to be considered as important factors, which may influence arithmetic performance (Temple and Sherwood, 2002).

4.3.1 Domain specificity vs. domain generality

The question of whether the difficulty in learning mathematics in DD is due to a single impairment or a combination of impairments in a more general cognitive system is still open. Currently, there exist two different models: Model 1 assumes that dyscalculia is due to a defective number module, a so-called impaired 'core deficit', the second, Model 2, characterizes DD as a consequence of deficits in domain-general cognitive abilities, such as memory, reasoning, or spatial abilities (Mix and Sandhofer, 2007; von Aster and Shalev, 2007).

The domain specific model about 'core knowledge' endows infants with core knowledge for number (Spelke, 2003; Wynn, 1992; Wynn, 1998). It is proposed that two core systems for representing number exist. One system represents number in an exact way but has a fixed upper limit (Feigenson et al., 2002; Starkey and Cooper, 1980); the other system has no size limit but represents number only approximately (McCrink and Wynn, 2004; Xu and Spelke, 2000). Both systems are claimed to have a phylogenetic origin, an innate number sense, and to constitute the basis for ontogenetic development. As already mentioned in chapter 3, the neural system for representing approximate numerical magnitudes including the "number sense" is associated with the bilateral horizontal segment of the intraparietal sulcus (HIPS). Wilson and Dehaene (2007) claim that at least some types of dyscalculia may be due to an impairment of functioning and/or structure in the HIPS, and/or in its connections to other numerical cognition regions.

On the other hand, investigators favouring Model 2 suggest that domain general processes are essential and domain specific processes cannot function without them. This domain-general approach assumes that infants are born without domain specific knowledge, but acquire such knowledge as a function of domain general processes (Courage and Howe, 2002). Examples of domain general functions might include processing speed and working memory. They further define domain general abilities as cognitive abilities that influence performance across a wide range of situations or domains.

In a review, entitled 'Do we need a number sense', Mix and Sandhover (2007) accentuate that research of early concepts focuses on the development of domain specific factors and little interest is given on domain general processes. These domain-general factors co-occur in any field of number and arithmetic and therefore, these processes must play a central role and contribute to numerical development (von Aster and Shalev, 2007).

In principle, one has to consider that in contrast to adult cognition, where domain specificity has already emerged, the developing brain underlies different aspects that contribute to specific knowledge. However, studying cognitive development, such as the acquisition of number and arithmetical knowledge, and studying its disorder, requires both, the investigation of domain specific and domain general processes.

4.4 Neural Correlates of Developmental Dyscalculia

In contrast to the amount of knowledge about the neural underpinnings of number processing in typically performing adults and children, only few studies investigated brain anatomy and function in population with impaired number processing capacities.

Less activation in the frontoparietal network during number processing was reported in populations with chromosomal disorders and abnormal numerical representations (Molko et al., 2003). Recently, Kucian and colleagues (2006) presented the first attempt of characterizing the neural underpinnings of developmental dyscalculia in affected children by means of fMRI. Results indicated weaker brain activation in almost the entire neuronal network for analog number processing in dyscalculic children. In general, dyscalculic and typically achieving children activated similar brain regions during number processing. Evidence of parietal dysfunction in DD is also shown by Price and colleagues (2007) – they consider these specific abnormalities in the functional neuroanatomy as being involved in the impaired numerical magnitude processing in DD.

Isaacs and colleagues (2001) used voxel-based morphometry to compare grey matter density in two groups of preterm-born adolescents. The target group suffered from arithmetical problems, while the control group showed normal calculation abilities. The left intraparietal sulcus was the most prominent region with reduced grey matter density in the dyscalculic group. The authors concluded that this area is the neural correlate of arithmetical impairments in the examined adolescents. However, the degree to which this finding can be extended to children who were not born very prematurely still remains to be discovered (Dowker, 2006A; Isaacs et al., 2001).

5. General aims and Hypotheses

The following general aims and hypotheses for the two studies of the thesis were developed:

Two complementary brain imaging tools (VBM and fMRI) were applied to investigate the underlying neural mechanisms of DD. Specific emphasis was given to favour either the domain specific or domain general model of DD.

General aim 1 (Study A): To assess brain anatomy of children with DD and normally achieving children by use of Voxel Based Morphometry.
In accordance with reported morphological and functional conspicuities in the IPS of subjects with calculation disabilities we hypothesize reduced grey and white matter volume in dyscalculic children at the IPS. The domain specific hypothesis predicts that the IPS is exclusively impaired in dyscalculic with DD, the domain general approach predicts additional frontal and cingulate brain regions to be affected in children with DD.

General aim 2 (Study B): To further investigate the general domain hypothesis, in this second study, special interest is addressed to a domain general factor, spatial working memory. We compare neural brain activation of children with and without DD during a spatial working memory task.
We hypothesize that dyscalculic children show weaker activation at frontal and parietal areas compared to control children in association with spatial working memory operations.

6. Study A: Optimized Voxel-Based Morphometry in Children with Developmental Dyscalculia

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6.1 Abstract

Developmental dyscalculia (DD) is a specific learning disability affecting the normal acquisition of arithmetic skills. Current studies estimate that 3-6% of the school population is affected by DD. Genetic, neurobiological and epidemiologic evidence indicates that dyscalculia is a brain-based disorder. Imaging studies suggest the involvement of parietal and prefrontal cortices in arithmetic tasks.

The aim of the present study was to analyze if children with DD show structural differences in parietal, frontal, and cingulate areas compared to typically achieving children.

Magnetic resonance imaging was obtained from 12 children with DD aged 9.3 ± 0.2 years and 12 age-matched control children without any learning disabilities on a 1.5 T whole-body scanner. Voxel-based morphometry analysis with an optimization of spatial segmentation and normalization (OVBM) procedures was applied to compare the two groups in order to find differences in cerebral grey and white matter.

Compared to controls, children with DD showed significantly reduced grey matter volume in the right intraparietal sulcus, the anterior cingulum, the left inferior frontal gyrus, and the bilateral middle frontal gyrus. White matter comparisons demonstrated clusters with significantly less volume in the left frontal lobe and in the right parahippocampal gyrus in dyscalculic children.

A neural equivalence to number processing capacities constitutes the grey matter volume decrease in the right intraparietal sulcus – but volume differences in frontal regions, especially the anterior cingulum, refer to possible prior impairments of the attentional and working memory system, which might have negative effects on the acquisition of number representation and number processing capacities.

6.2 Introduction

Children with developmental dyscalculia (DD) show a significant discrepancy between specific math performance and general intelligence that cannot be explained by mental retardation, inappropriate schooling or poor social environment. The prevalence of developmental dyscalculia is 3 to 6% in the school-aged population. Unlike other learning disabilities little is known about its underlying neural mechanisms (Schweiter et al., 2005). Current data indicate that this learning disability is a brain-based disorder (Alarcon et al., 1997; Dellatolas et al., 2000; Kucian et al., 2006; Shalev and Gross-Tsur, 2001; Shalev et al., 2001).

The underlying brain processes of arithmetic performance in adults are well studied. Functional brain imaging (fMRI) studies with typically achieving adults have identified a number of brain regions involved in the performance of arithmetic tasks (Dehaene et al., 1999; Kawashima et al., 2004; Rivera et al., 2005; Rueckert et al., 1996). Dehaene and colleagues (2003) describe the horizontal segment of the intraparietal sulcus (HIPS) as the region most specifically involved in number representation. Activation of this region is observed in many different number processing tasks (Pinel et al., 2001), especially when nonverbal representation of numerical quantity, conceptualized as “mental number line”, is required. However, the network of areas activated during number processing includes frontal and anterior cingulate components as well (Chochon et al., 1999). These areas are related to working memory and visuospatial attention (Corbetta et al., 1993; D'Esposito et al., 2000; Postle et al., 2000).

FMRI studies of numerical processing in typically achieving children revealed similar functional networks compared to adults (Cantlon et al., 2006; Kawashima et al., 2004; Rivera et al., 2005). However, children primarily engaged frontal regions, suggesting that children require comparatively more working memory and/or allocation of attentional resources to complete a calculation task. Adults, on the other hand, showed an increased activation in parietal areas referring to a functional specialization for the processing of mental arithmetic and numerical magnitude over age (Ansari and Dhital, 2006; Ansari et al., 2005; Rivera et al., 2005).

In contrast to the amount of knowledge about the neural underpinnings of number processing in typically performing adults and children, only few studies investigated brain functions in populations with impaired number processing capacities. Less activation in the frontoparietal network during number processing was reported in populations with chromosomal disorders and abnormal numerical representations (Molko et al., 2003). But the genetic origin of these two disorders should not be disregarded and the question to what extent these disorders lead to developmental dyscalculia is still open.

Recently, Kucian et al. (2006) presented the first attempt of characterizing the neural underpinnings of developmental dyscalculia in affected children by means of fMRI. Results indicated weaker brain activation in almost the entire neuronal network for analog number processing in dyscalculic children. In general, dyscalculic and typically achieving children activated similar brain regions during number processing.

The investigation of children with DD poses a special challenge as the outcome of this disorder is very heterogeneous. This constitutes a serious problem in functional neuroimaging studies because one task is not able to address the whole spectrum of impairments. Indeed, a great variety of non-specific problems, including slow speed of processing, poor working memory span, problems of attention, and deficits in the long-term storage of arithmetic facts have to be considered as an important factor, which may influence arithmetic performance (Temple and Sherwood, 2002).

Brain activation patterns demonstrated by fMRI are strongly task dependent, whereas voxel-based morphometry focuses on global structural differences independent of paradigm design or performance. Isaacs and colleagues (2001) used voxel-based morphometry to compare grey matter density in two groups of preterm-born adolescents. The target group suffered from arithmetical problems with otherwise normal IQ, while the control group showed calculation abilities consistent with IQ. The left intraparietal sulcus was the most prominent region with reduced grey matter density in the dyscalculia group. The authors concluded that this area is the neural correlate of arithmetical impairments in the examined adolescents. However, the degree to which this finding can be extended to children who were not born very prematurely still remains to be discovered (Dowker, 2006; Isaacs et al., 2001). To answer this question, we investigated term-born children with developmental dyscalculia and typically achieving children by using optimized voxel-based morphometry (OVBM), a voxel-wise comparison of local ratios of grey matter (GM) and white matter (WM). We expected structural differences in parietal areas of children with developmental dyscalculia in accordance to reported morphological and functional conspicuities in the IPS of subjects with calculation disabilities. Furthermore, we assumed the entire neuronal network for number processing, including parietal, frontal, and cingulate areas, as described in several fMRI studies in typically achieving and dyscalculic subjects to be altered in dyscalculic children (Chochon et al., 1999; Kucian et al., 2006).

6.3 Materials and Methods

Subjects

We used OVBM to analyze T1-weighted magnetic resonance images (MRI) of 12 children with DD (6 male, 6 female, mean age 9.3 ± 0.2 years). Participants were healthy, right-handed volunteers with no psychiatric or medical complications as determined by a detailed questionnaire. None of the children suffered from any neurological abnormalities and all were medication free. Dyscalculia was clearly diagnosed by trained specialists, e.g. by psychological school services, according to the ICD-10 manual (Specific disorder of arithmetical skills, F81.2) (WHO, 2005). Tests to assess their mathematical, linguistic and spatial abilities as well as their IQ were conducted [ZAREKI (von Aster, 2001); K-ABC (Kaufman and Kaufman, 1994); HAWIK-III (Wechsler, 1999)]. None of the children had other diagnosed co-morbidities (e.g. dyslexia, ADHD).

Twelve typically achieving children from public school (6 females, 6 males, mean age 9.7 ± 0.2 years) served as age- and gender matched control group. None of these children suffered from any neurological, psychiatric or learning disorder. Children were tested for number processing and calculation abilities [ZAREKI (von Aster, 2001)] and for reading and spelling skills [Knuspel's Leseaufgaben (Marx, 1998); Salzburger Lese- und Rechtschreibtest (Landerl et al., 1997)]. All children showed normal age-related performance compared to a Swiss normative sample of 337 age-matched children, indicated in italics [ZAREKI: 147.5 (21.9); *143.6 (27.7)*; Knuspel's Leseaufgaben: 26.5 (2.9); *21.2 (8.6)*; Salzburger Lese- und Rechtschreibtest: 8.0 (1.7); *7.53 (4.2)*].

Written, informed consent for the participation in this study was obtained from the legal guardians of the children. The study was approved by the local ethics committee based on the World Medical Association's Declaration of Helsinki (WMA, 2002).

Image acquisition

MRI acquisition was performed on a 1.5 Tesla whole-body system (Signa Twinspeed Excite, GE Healthcare, Milwaukee, WI, USA). Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted gradient echo pulse sequence (TR

= 25 ms; TE = 5 ms; FOV = 220 mm x 220 mm x 170 mm; image resolution = 1.72 mm x 1.72 mm x 1.70 mm).

Optimized voxel-based morphometry

Data were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk) on MATLAB 6.5 (The MathWorks, Natick, MA, U.S.A.). Voxel-based morphometry as proposed by Ashburner and Friston (2000) involves a voxel-wise comparison of the local concentration of grey and white matter between two groups of subjects. This standard pre-processing protocol tends to result in misinterpretations of structural differences as a result of normalization, which are not directly related to grey or white matter volumes (Mechelli et al., 2005). We used the optimized VBM protocol, as described by Good et al. (2001) and a special-purpose scripting tool with modulation (http://dbm.neuro.uni-jena.de/vbm.html) to minimize this potential source of error by performing the normalization using the segmented grey and white matter volumes rather than the whole brain volumes. With this adjustment, VBM can be thought of as comparing the absolute volume of grey or white matter structures. We performed the OVBM in a two-stage process: (1) Customized GM and WM templates were created to reduce scanner- and population-specific biases. Templates were linear-spatially normalized to a standardized anatomical space using an age-matched brain template (CCHMC pediatric brain template, http://www.irc. cchmc.org/ped_brain_ templates.htm) to further improve spatial normalization. Normalized brain volumes were segmented into GM, WM and cerebrospinal fluid (CSF) volumes and smoothed with a full-width at half-maximum Gaussian kernel of 8 mm. (2) Each segmented volume was non-linearly normalized to the customized template; resulting normalization parameters were applied to the original brain volumes. Non-linearly normalized brain volumes were afterwards segmented and modulated for comparison of volume effects. Thereafter, GM and WM segments were spatially smoothed with a full-width at half-maximum Gaussian kernel of 12 mm. Finally voxel-wise between group comparisons of the smoothed GM and WM volumes were performed using a two sample t-test within SPM2. Reported results represent uncorrected p values of <0.001 on the voxel level restricted to clusters of >70 voxels, which is equivalent to corrected cluster-levels of $p < 0.001$.

6.4 Results

Voxel-based Morphometry

Grey matter

ANOVA comparisons demonstrated clusters with significantly less grey matter volume for dyscalculic children in frontal lobe regions: the bilateral anterior cingulum, the right and left middle frontal gyrus and the left inferior frontal gyrus (Fig. 1A and Table 1), as well as in the right intraparietal sulcus (Fig.1B and Table 1).

No cluster of increased grey matter volume was found in dyscalculic children when compared to control children.

Table 1 Grey matter volume changes in dyscalculic children

Anatomical region	Hemisphere	Talairach coordinates			p value corrected Cluster level	T score Voxel level	Number of voxels in cluster (k_E)
		x	y	z			
Anterior cingulum	Right	11	43	2	<0.001	5.09	5487
Anterior cingulum	Left	-11	40	2	<0.001	4.97	4660
Middle frontal gyrus	Right	45	41	-11	<0.001	3.98	1644
Middle frontal gyrus	Left	-43	37	-11	<0.001	4.47	7476
Inferior frontal gyrus	Left	-55	45	2	<0.001	5.41	7476
Intraparietal sulcus	Right	22	-45	55	<0.001	5.25	766

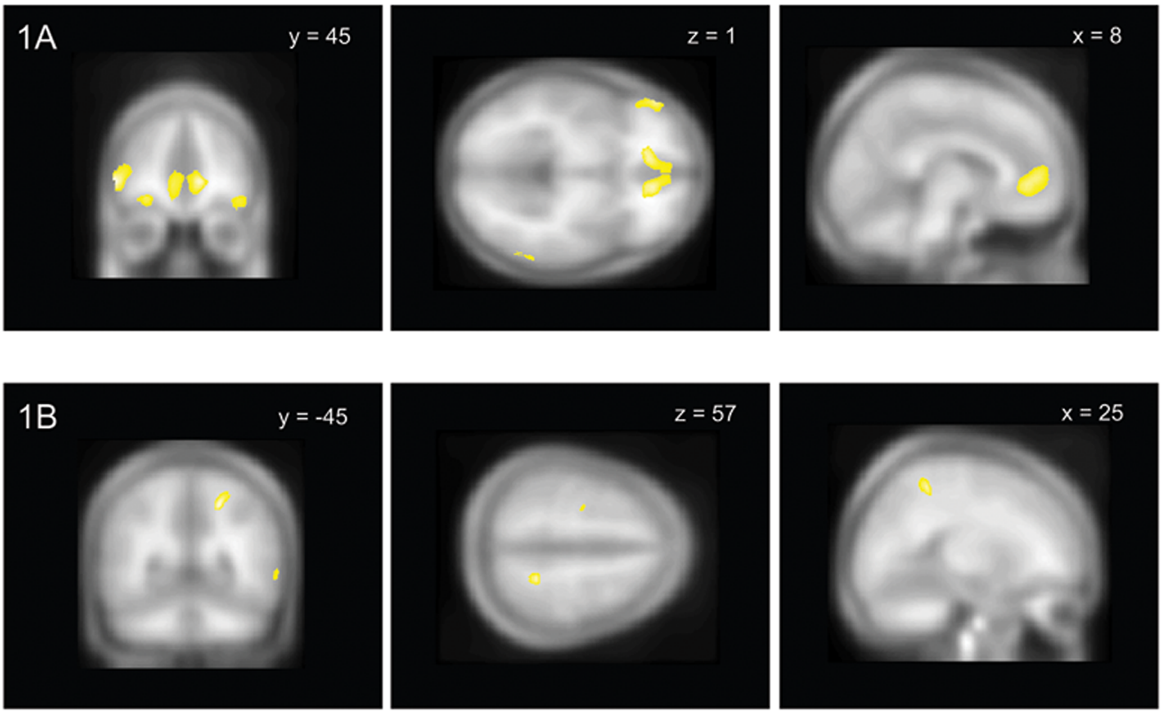

Figure 1A Frontal regions of decreased grey matter volume in children with DD compared to controls (cluster level corrected p<0.001).

Figure 1B Parietal region of decreased grey matter volume in children with DD compared to controls (cluster level corrected p<0.001).

White matter

ANOVA white matter comparisons demonstrated clusters with significantly decreased white matter volume in the left frontal lobe and adjacent to the right parahippocampal gyrus for dyscalculic children (Fig. 2 and Table 2).

Dyscalculic children did not show regions of significantly increased white matter volume.

Table 2 White matter volume changes in dyscalculic children

Anatomical region	Hemisphere	Talairach coordinates			p value corrected Cluster level	T score Voxel level	Number of voxels in cluster (kE)
		x	y	z			
Parahippocampal Gyrus – white matter	Right	25	-9	-14	<0.001	5.11	4579
Frontal lobe - subgyral	Left	-16	43	-19	<0.001	5.06	5317

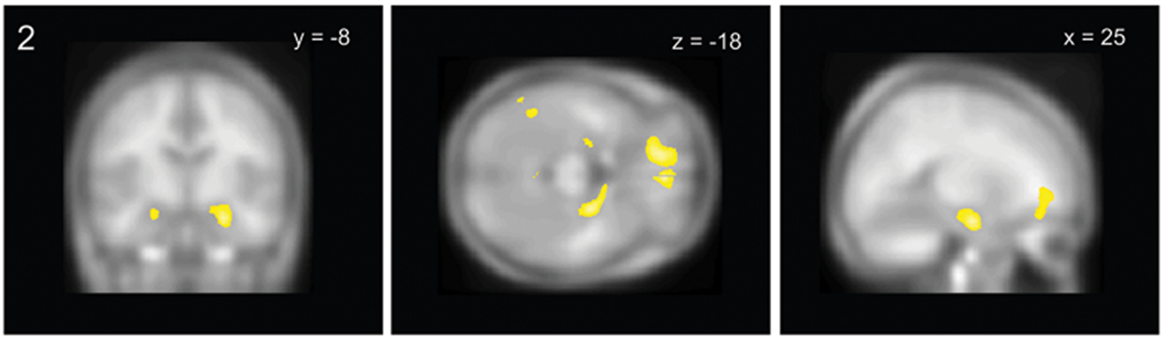

Figure 2 Frontal and parahippocampal regions of decreased white matter volume in children with DD compared to controls (cluster level corrected *p*<0.001).

6.5 Discussion

The aim of the present study was to identify differences in brain structures of dyscalculic children without any co-morbid diagnosis. A number of brain-imaging studies have implicated the frontal and parietal cortices in arithmetical processing (Chochon et al., 1999; Rickard et al., 2000). Therefore, we hypothesized that children with DD show structural differences in parietal and frontal areas when compared to typically achieving children.

In the present study, children with dyscalculia show decreased grey matter volume in the right IPS compared to the control group, while the left IPS shows no volume differences. The VBM study of Isaacs and colleagues (2001) identified only one region of decreased grey matter volume in the left intraparietal sulcus in preterm-born adolescents with calculation deficits. However, they discuss the possibility of a whole network of regions relevant for number processing being affected. These regions include the homologous area in the right parietal lobe as well as frontal areas. One study in patients with Turner Syndrome and arithmetic impairments demonstrated a morphologically abnormal length, depth, and sulcal geometry of the right IPS and reduced neural activation of this region as a function of number size (Molko et al., 2003). A recent transcranial magnetic stimulation study pointed to the possible involvement of the right IPS in dyscalculia (Cohen Kadosh et al., 2007). Overall, reported laterality of parietal conspicuities are inconsistent. This variation of affected hemispheres may be a result of differences between examined patient groups, used tasks or the age of subjects.

The developmental study of Rivera et al. (2005) reports, that brain activation during calculation changes with age. The authors conclude, that their findings provide evidence for a process of increased functional specialization of the left inferior parietal cortex in mental arithmetic, a process that is accompanied by decreased dependence on memory and attentional resources with development (Rivera et al., 2005). Our morphological results support this assumption - grey matter volume differences in parietal regions between our two groups are not as distinctive as expected; there is only one region within the right IPS where typically achieving children show more grey matter than dyscalculic children. Following, we assume that the parietal brain areas required for arithmetical processing are not fully developed in our children population. This is in good accordance with another developmental fMRI study investigating adults and children during magnitude judgment (Ansari et al., 2005). Whereas numerical distance modulates parietal regions in adults, children primarily engage frontal regions. The authors conclude that the functional neuroanatomy underlying symbolic numerical magnitude processing undergoes an ontogenetic shift towards greater parietal engagement. Additionally, younger subjects require comparatively more working memory and attentional resources to achieve similar levels of mental arithmetic performance (Rivera et al., 2005). Based on the fact that children with arithmetical disability have a specific working-memory deficit in relation to processing numerical information (Siegel and Ryan, 1989) and that an important component in the development of arithmetical skill is the growth of working memory for numerical information, the grey matter volume differences found in our group at the bilateral middle frontal gyrus, the left inferior frontal gyrus and bilateral anterior cingulum may be of major importance in the development of dyscalculia. These findings refer to possible prior sub-clinical impairments of the attentional and the working memory system, which might have a negative effect on the acquisition of number representation and number processing capacities. Besides, general brain development is not finished at the age of 7 to 9 years. Therefore, comparisons of morphological as well as fMRI data between dyscalculic children and adults should be drawn carefully (Wilke et al., 2007).

In addition to grey matter differences, we observed decreased white matter volume of the right parahippocampal gyrus, a region known to play a major role in fact retrieval and spatial memory processes (Stern et al., 1996). These white matter volume differences further support the assumption that deficits in neuronal networks important for fact retrieval might hamper the development of adaptive number representations in children with developmental dyscalculia.

In conclusion, our results provide new insights into the underlying anatomical conspicuities in dyscalculic children. Morphological differences in frontal brain areas of children with DD point to missing auxiliary functions, like working memory, interference control and strategic planning. These impaired processes might influence the development of dyscalculia.

6.6 Acknowledgement

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7. Study B: Dysfunctional Neural Network of Spatial Working Memory Contributes to Developmental Dyscalculia

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7.1 Abstract

The underlying neural mechanisms of developmental dyscalculia (DD) are still far from being clearly understood. Even the behavioural processes that generate or influence this heterogeneous disorder are a matter of controversy. To date, the few studies examining functional brain activation in children with DD mainly focus on number and counting related tasks, whereas studies on more general cognitive domains that are involved in arithmetical development, such as working memory are virtually absent. There are several studies showing a close relationship between DD and spatial working memory (Camos, 2008; McLean and Hitch, 1999; Rosselli et al., 2006; Siegel and Ryan, 1989). The relationship between these two mechanisms is still matter of debate, but this study follows the assumption that poor spatial working memory capacity may hinder the acquisition of spatial number representations in children with DD (Geary, 1993; von Aster and Shalev, 2007).

Using functional MRI the current study compares brain activity associated with spatial working memory processes in 8 to 10 year old children with DD and normally achieving controls. Both groups showed significant spatial working memory related activity in a network including occipital and parietal regions. Children with DD showed weaker neural activation compared to the control group during a spatial working memory task in the right intraparietal sulcus (IPS), the right insula and the right inferior frontal lobe. Performance tests outside the scanner showed impaired working memory proficiency in children with DD. Bringing behavioural performance and neural activity together we found significant correlations of right IPS activity with performance on the verbal digit span forward and the spatial Corsi Block Tapping test.

Our findings demonstrate for the first time an involvement of spatial working memory processes in the neural underpinnings of DD. These poor spatial working memory processes may inhibit the formation of spatial number representations (mental numberline) as well as the storage and retrieval of arithmetical facts.

7.2 Introduction

Developmental Dyscalculia (DD) is characterized by difficulties representing and manipulating numerical information nonverbally and visuospatially, in learning and remembering arithmetic facts and in executing arithmetic procedures. DD in children has a prevalence of 3 to 6% in the school aged population, what is comparable to dyslexia, and high rates of comorbidities, such as ADHD (Koumoula et al., 2004; Shalev et al., 2000). Yet little is known about the underlying deficits. The question of whether this difficulty in learning mathematics is due to a single impairment of a basic number specific core competence ('number sense') or a combination of impairments in a more general cognitive system is still open (Butterworth, 2004; Mix and Sandhofer, 2007). One impediment to research on DD is the complexity of the numerical domain that includes verbal, visuo-spatial, memory, and executive functions (Ardila et al., 1998; Geary et al., 2000; von Aster, 2000). This wide array of cognitive factors that could contribute to DD poses a special challenge to investigate this disorder.

Deficits in working memory systems have been argued to substantially contribute to specific deficits in building cognitive representations of number, the formation of concepts and procedures as well as arithmetic fact retrieval in children with DD (Geary, 1993; von Aster and Shalev, 2007). Working memory refers to the mental capacity responsible for the temporary processing and storage of information (Rosselli et al., 2006). It requires both the simultaneous processing of incoming and the retrieval or manipulation of retained information (Siegel and Ryan, 1989). This capacity for information processing is limited, since higher demands on the former will negatively influence the access to the latter, and vice versa. Therefore, variation in this capacity is related to performance in any cognitive activity (Camos, 2008), including arithmetics.

Several studies investigated the role of working memory in typically achieving children and children with DD (Bull et al., 2008; D'Amico and Guarnera, 2005; Geary et al., 2000; Geary and Hoard, 2001; McLean and Hitch, 1999; Rosselli et al., 2006; Siegel and Ryan, 1989). Van der Sluis and colleagues (2005) showed that children with arithmetic disabilities performed worse on a task requiring the memorization of dynamic visual information – these results are consistent with other findings (McLean and Hitch, 1999), reporting lower performance of children with arithmetic disabilities on the Corsi Block Tapping task. Concerning the different aspects of working memory, children with poor arithmetic performance generally appear to have normal phonological working memory (McLean and Hitch, 1999; Siegel and Ryan, 1989), although their capacity of spatial working memory is impaired.

A broad network of regions including predominantly frontal and parietal regions modulates spatial working memory. Children performing visuospatial working memory tasks show the same, but decreased activation pattern compared to adults, especially the dorsolateral prefrontal cortex is less recruited (Klingberg et al., 2002; Kwon et al., 2002; Nelson et al., 2000; Scherf et al., 2006).

To date, only a few studies have investigated children with DD by means of anatomical or functional brain functions. Kucian and colleagues (2006) showed that children with DD have weaker brain activation in the IPS and the middle and inferior frontal gyrus of both hemispheres for approximate calculation than typically achieving children. Evidence of parietal dysfunction in DD has also been reported by Price and colleagues ((Price et al., 2007). In a recent study investigating structural brain volume in children with and without DD Rotzer and colleagues (2008) found reduced grey matter volumes in frontal and parietal regions. Hence, the question arose whether these differences are related to specific number processes or whether they may be attributed to more domain general factors such as working memory and attention.

The current study aims, for the first time, to compare the functional neuroanatomy of children with and without DD while performing a spatial working memory task. We hypothesize that children with DD show weaker activation in brain areas related to spatial working memory, such as the frontal and parietal cortex, since children with DD seem to have impaired spatial working memory capacities that are modulated by frontal and parietal brain regions.

7.3 Methods

Participants

The study included 11 girls and 3 boys with the diagnosis of developmental dyscalculia and 12 age matched controls with age appropriate calculation performance (ZAREKI-R (von Aster et al., 2006)). None of the participants had neurological or psychiatric disorders. They were not on medication and had no exclusion criteria for MRI. Five children were not included - two children with DD refused scanning, another two children with DD and one control child showed less than 60% accuracy rate within the scanner task. The remaining group included ten children with DD (8 female, 2 male; mean age 10.4; SD, 1.2) and eleven controls (9 female, 2 male; mean age, 10.2; SD, 1.0). Parents gave informed consent and children received a voucher for their participation. The study was approved by the local ethics committee based on the World Medical Association's Declaration of Helsinki (WMA, 2002).

Behavioral Testing

Behavioral evaluation was carried out during two sessions before scanning. Mental ability was measured with three verbal (Vocabulary, Arithmetic, Similarities) and two performance subtests (Picture Arrangement, Block Design) of the Wechsler Intelligence Scale for Children (HAWIK-III) (Wechsler, 1999), (population mean = 100, SD = 15). Handedness was examined through the Edinburgh Handedness Inventory (Oldfield, 1971). Numerical abilities were assessed using the Neuropsychological Test Battery for Number Processing and Calculation in Children (ZAREKI-R). This neuropsychological battery examines the progress of basic skills in calculation and arithmetic and identifies and characterizes the profile of mathematical abilities in children with dyscalculia. It's composed of 11 subtests, such as reverse counting, subtraction, number reading, dictating, visual estimation of quantities, digit span forward and backward. Criteria for developmental dyscalculia were met if a child's performance in the ZAREKI-R was 1.5 SD below average in three subtests or in the total score. Spatial working memory performance was measured with the Corsi Block Tapping test, a test assessing spatial working memory span. On a board with 9 cubes, the examiner taps the cubes in a given sequence. Subjects are required to repeat the cube sequences in the same order immediately after the examiner has finished. While the sequences gradually increase in length, the number of cubes last tapped on in two consequently correct sequences is defined as maximum span. Children were also tested on the Block Suppression Test (Beblo et al., 2004) – this test is based on the Corsi Block tapping test and requires the subject reproducing every 2nd block in a given sequence (Beblo et al., 2004). This task requires children to suppress irrelevant spatial information actively.

Paradigm Design

The scanner paradigm is an adaptation of the Corsi Block Tapping test (Klingberg et al., 2002). Participants were asked to remember the location of three red dots, which were presented sequentially in a 4 × 4 grid, each dot for 2333 ms. After a delay period of 1500 ms, a red circle appeared for 1500 ms and they had to press a button with their right index finger when the circle was in the same location as any of previously presented dots. If not, they had to press another button with their right middle finger. The control condition used the same stimuli as the working memory task, but with green dots. Children just had to watch the dots and to press a button when a green circle appeared. Three working memory trials (red dots) alternated with three control trials (green dots) for three times. The presentation order was counterbalanced across subjects. The time between conditions was jittered between 5000 ms and 15000ms. Subjects were carefully instructed about the experimental procedure and had to practice trial tasks, before entering the scanner.

Image Acquisition

Brain images were acquired on a 3.0 T whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) using a standard 8-channel head coil. Scan parameters were number of slices (NS): 36 (parallel to the AC-PC line); slice thickness (ST): 3.4 mm; matrix size (MS): 64 × 64; field of view (FOV): 220 mm × 220 mm; flip angle (FA): 45°; echo time (TE): 31 ms; repetition time (TR): 2100 ms. The task was presented via video goggles (MRI Audio/Video System, Resonance Technology, Inc., USA) using E-Prime software (Psychology Software Tools Inc.). Three-dimensional anatomical images of the entire brain were obtained by using a T1-weighted gradient echo pulse sequence (NS= 172, ST= 2.0 mm, TR = 9.988 ms, TE= 2.916 ms, FOV = 240 mm× 240 mm, FA: 20°, MS = 256 × 192).

Data Analysis

Behavioral Data

Two-sample t-tests and non-parametric Mann-Whitney tests were used as planned comparisons to evaluate behavioural tests outside the scanner. Non-parametric Mann-Whitney tests were used to evaluate mean response times (red and green circles) and accuracy rate of the scanner task. All statistical procedures were performed with the "Statistical Package for the Social Science 14.0" (SPSS 14.0).

Imaging Data

Functional images were analyzed with statistical parametric mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Brain volumes for each individual were spatially realigned and unwarped. No child had to be removed from the study because of movement artefacts (maximum movement of less than one image-pixel size). A mean functional image volume was constructed for each participant for each session from the realigned image volumes. These mean images were then segmented using an age-matched grey matter brain template (Cincinnati: http://www.irc.cchmc.org/software/pedbrain.php) and normalization parameters were estimated during the segmentation process. These normalization parameters were applied to the original functional brain images for spatial normalization on the children template. Normalized images were smoothed with a 9 mm^3 full width at half maximum Gaussian filter.

To generate statistical maps for each subject we modelled the expected hemodynamic response for the working memory and control task with a canonical hemodynamic response function, and its temporal and dispersion derivative. The functions were convolved by the event train of stimulus onsets of every dot to create covariates in a general linear model. Three scans were discarded to accommodate for T2 saturation. Parameter estimates for each covariate were obtained by maximum-likelihood estimation while using a temporal high-pass filter (cut-off 128 s) and modelling temporal autocorrelations as an AR(1) process. For group analysis, we conducted the SPM5 implemented standard whole brain second-level random effects analysis. First, we computed one-sample t-tests for each group to reveal activations for spatial working memory (working memory > control task). Significant voxels are reported at a threshold of $p<0.0001$, uncorrected. Second, to detect the effect of DD, we computed group comparisons with two sample t-tests between children with DD and control children. Significant activation differences between groups are identified at $p < 0.001$, uncorrected.

To specify and illustrate the fMRI signal, a non-independent correlation analysis was conducted. Region of Interests (ROI) based on the significant differences between cohorts (working memory > control task, $p<0.001$) were defined: at the right intraparietal sulcus (IPS) (36/-42/51), the right insula (45/-3/6) and right inferior frontal gyrus (33/42/0). ROI spheres of 8mm radius were produced and ROI analyses were performed using the MarsBar toolbox (http://marsbar.sourceforge.net/) in SPM5. For each participant percent BOLD signal change was extracted and correlated with behavioral data of working memory tests and calculation tests. All data are reported in Montreal Neurological Institute (MNI) stereotactic space.

7.4 Results

Behavioral Performance (outside the scanner)

Mean scores and standard deviations for tests are presented in Table 1. All subjects scored an intelligence quotient (IQ) of 97 or more on the HAWIK-III subtests. This means that all children were within the average range and there was no significant group difference in estimated total subtests IQ and estimated performance IQ but there was a significant difference in estimated verbal IQ (see table 1). Analysis of the ZAREKI-R of children with DD showed significant different percentile ranges compared to normally achieving children at different subtests and the total score (see table 1). Table 1 shows also lower performance of the children with DD compared to the control children in all working memory tasks (Corsi Block Tapping test, Block Suppression test and digit span forwards) except of digit span backwards.

Table 1 Demographic and clinical characteristics

	Dyscalculic Group (N=10)		Control Group (N=11)		Analysis
Handedness (N: right / ambidexter / left)	(5/4/1)		(9/2/0)		
	Mean	SD	Mean	SD	t-test
Age	10.4	1.2	10.2	1.0	$p > 0.5$
Total IQ	103.7	5.3	109.4	6.7	$p > 0.06$
Verbal IQ	103.2	8.6	110.7	7.2	$p < 0.05$
Performance IQ	104.8	6.9	107.5	8.8	$p > 0.4$
ZAREKI-R, “addition” (percentile rank (PR))	33.3	36.4	80.9	31.0	$p < 0.05$
ZAREKI-R, “number writing” (PR)	36.1	44.5	90.6	21.5	$p < 0.05$
ZAREKI-R, “subtraction” (PR)	9	17.0	70.0	30.8	$p < 0.001$
ZAREKI-R, “number comparison words” (PR)	37.6	43.9	75.6	32.5	$p < 0.05$
ZAREKI-R, total (PR)	17.6	29.3	69.1	21.9	$p < 0.01$
Corsi Block Tapping Test	4.5	0.7	5.3	1.0	$p < 0.05$
Block Suppression Test	1.9*	1.0	3.1	1.2	$p < 0.05$
Digit span forwards	4.4	0.70	5.3	0.79	$p < 0.05$
Digit span backwards	3.0	0.67	3.5	0.82	$p > 0.05$

Behavioral Performance (inside the scanner)

Behavioral data during scan session demonstrated that all subjects had equivalent performance on the working memory task regarding reaction time ($p > 0.42$) and accuracy rate ($p > 0.49$).

fMRI Results

In control children the working memory task elicited greater activation when compared with the control task in the following network: bilateral middle occipital, superior and intraparietal and cerebellar regions, but also the left inferior and the right middle frontal gyrus, the left thalamus and the basal ganglia.

Children with DD, on the other hand, activated clusters in the right inferior occipital gyrus, the cuneus, the right precuneus and left superior, inferior and intraparietal cortex.

Three regions showed significantly greater activation for the working memory task in the control group compared with the dyscalculic group. Control children showed significantly enhanced activation in the right inferior frontal lobe, the right insula and in the right IPS. There were no regions that showed significantly greater activation in the dyscalculic group compared to the control group.

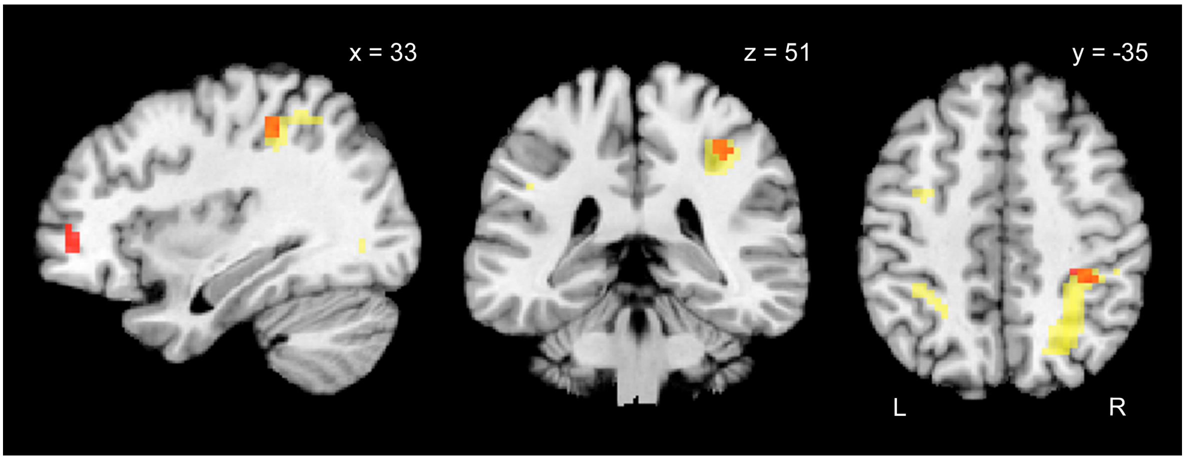

Figure 1 Statistical maps overlaid onto a reference high-resolution anatomical brain image (Colin27 brain, MNI Montreal). Displayed are the within-subject contrasts for control children (yellow, voxel level uncorrected $p < 0.0001$) and between-subject contrasts (red, control children > dyscalculic children, voxel level uncorrected $p < 0.001$) for the contrast between spatial working memory and the control task.

Table 2 Regions of significant activation during spatial working memory task in control and dyscalculic children. Listed are peak voxels ($p_{uncorrected} < 0.0001$). (L = left, R = right).

Region of activation	MNI coordinates			T score Voxel level	Number of voxels in cluster (k_E)
	x	y	z		
Control group					
R middle occipital gyrus	48	-78	-15	9.07	87
L middle occipital gyrus	-36	-90	9	6.85	36
R superior and intraparietal cortex	27	-60	57	10.19	125
L superior and intraparietal cortex	-27	-48	45	7.91	116
L inferior frontal gyrus	-33	36	6	7.37	37
R middle frontal gyrus	24	-6	66	8.36	22
L putamen	-27	9	0	6.39	59
L caudatus	-18	18	3	11.6	290
R cerebellum	24	-69	-33	8.92	110
L cerebellum	-18	-48	-27	10.28	172
L thalamus	-12	-24	15	9.57	373
Dyscalculic group					
R cuneus	33	-75	30	8.25	235
L cuneus	-24	-93	-6	12.84	439
R lingual gyrus	21	-102	-12	11.12	116
R inferior occipital gyrus	42	-90	-15	8.83	159
L middle occipital gyrus	-51	-72	0	8.22	129
L superior and intraparietal cortex	-21	-63	69	11.71	344
R precuneus	24	-57	45	8.64	120
L inferior parietal lobe	-45	-45	54	8.9	27
R thalamus	12	-24	12	9.78	104
L putamen	42	-90	-15	8.83	159

Table 3 Regions showing significantly greater activation in control compared to dyscalculic children. Listed are peak voxels (p uncorrected < 0.001). (L = left, R = right).

Region of activation	MNI coordinates			T score Voxel level	Number of voxels in cluster (k_E)
	x	y	z		
R inferior frontal gyrus	33	42	0	4.19	22
R intraparietal sulcus	36	-42	51	3.52	13
R insula	45	-3	6	3.44	21

Non-independent ROI Analysis

A non-independent correlation analysis was conducted to discover which behavioral test significantly correlated with the three defined ROIs. It revealed that the Corsi Block Tapping test (p = 0.022) and digit span forward (p = 0.017) significantly correlated with the ROI in the IPS. The latter test correlated also with the ROI of the right Insula (p = 0.016). (see Figure 2). There were no other significant correlations with working memory tasks, calculation tests or the frontal ROI.

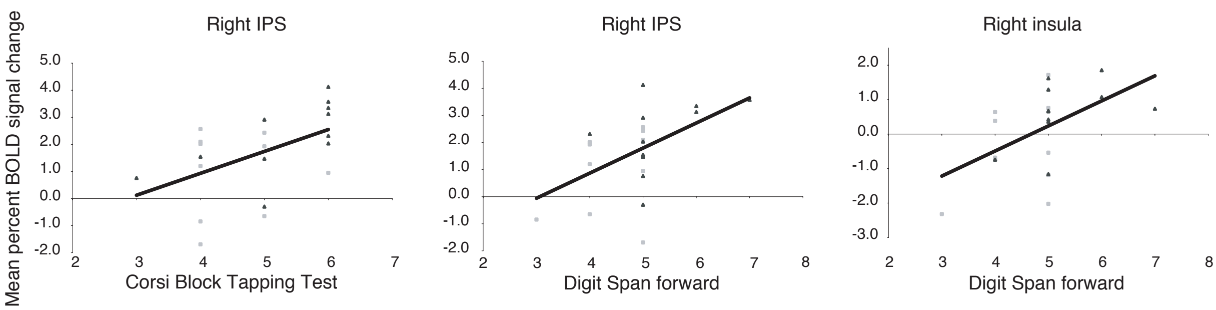

Figure 2 Significant correlations between behavioral test results (Corsi Block Tapping Test and the digit span forward) and mean percent BOLD signal change within regions of interest at the right IPS (x = 36, y = -42, z = 51) and the right insula (x = 45, y = -3, z = 6). (Grey squares = dyscalculic children, dark triangles = control children).

7.5 Discussion

Our study provides first evidence for significant changes in neural responses of underlying spatial working memory processes in dyscalculic children compared to normally achieving controls. Control children activated a broad network of bilateral middle occipital and bilateral superior and intraparietal areas during spatial working memory task. Moreover, they activated right middle and left inferior frontal areas, left thalamus and the cerebellum bilaterally. These findings are largely consistent with other studies (Smith and Jonides, 1999; Ungerleider and Haxby, 1994; Wager and Smith, 2003). In contrast to Klingberg and colleagues, we found no activation in the superior frontal sulcus (Klingberg et al., 2002). This region has been found to exhibit sustained activity during the delay period when information is held in WM. An explanation for this discrepancy in results may lie in the difference between tasks. Klingberg and colleagues used both low and high load conditions, in which three, respectively five dots had to be held in WM. We discarded the high load condition, because we expected children with DD to exhibit problems with high working memory load and aimed to minimize inter-individual and group differences in behavioural performance during scanning. Children with DD showed no activation clusters in frontal areas but additional clusters within the cuneus, bilaterally, and the right precuneus. Over all, activation clusters seem to be deviant from control children and may indicate a selective impairment of the dorsal stream. Nonetheless, the task was highly sensitive in terms of functional brain imaging. All children were performing above chance level (> 60% correct answers) and showed comparable reaction times, indicating that differences in functional brain activation are related to task and not to task difficulty. Additionally, fMRI revealed significant activation patterns associated with cognitive performance outside the scanner. Our results demonstrate reduced activation in working memory relevant brain areas, such as the right IPS, the right inferior frontal lobe and in the right insula in children with DD when compared to the control group. These activation differences are shown in relatively small clusters, which might be caused by the small group size, but they are in close relationship to spatial working memory processes (Bor et al., 2001; Klingberg, 2006; Smith et al., 1996).

Like in our VBM study (Rotzer et al., 2008), the right IPS plays a crucial role in the neural network of children with DD. Decreased activation in the right IPS of children with DD during a non-numerical spatial working memory task strongly argues for a central role of the right IPS in both working memory capacity and the acquisition of spatial number representations and arithmetic concepts. There is a recent study revealing atypical activation in the right intraparietal sulcus (Talairach coordinates: 33, -50, 52) during a non-symbolic, numerical magnitude processing task in children with DD (Price et al., 2007). The authors strengthen the hypothesis that DD is caused by ontogenetic disruption of the neural circuitry that supports fundamental representation of numerical magnitude. Our results might indicate that deficient spatial working memory lies at the core of difficulties in non-symbolic numerical magnitude processing.

In a recent study by McNab and colleagues (2008) a region including the right inferior frontal gyrus and the insula was identified to be associated with inhibition and working memory manipulations. The authors argue that such inhibition processes may play a role in resistance to distraction, which is linked to working memory or, alternatively, an involvement of working memory processes in inhibition tasks (Aron and Poldrack, 2005; Roberts et al., 1994). Therefore, our results may indicate that children with DD have specific impairments in inhibiting irrelevant information. This is in accordance the clinical observation of frequently associated symptoms of inattentiveness and distractibility in children with DD (von Aster and Shalev, 2007).

Complementary to these differences in neural activation clusters children with DD show significant deficits in working memory tests. The performance in the Corsi Block Tapping test, the Block suppression test, the subtest ‘subtraction’ of the ZAREKI-R and the digit span forward was significantly lower in children with DD compared to normally achieving controls. These results are in line with findings from other studies (Schuchardt et al., 2008). Visuo-spatial short-term memory span was found to be a predictor specifically of math ability. Correlation and regression analyses revealed visual short-term and working memory to specifically predict math achievement at each time point (Bull et al., 2008; Schuchardt et al., 2008).

D'Amico and Guarnera (2005) examined children with a battery of working memory tests, and found that dyscalculic children showed a deficit in digit span forward, but only when the representation of numerical information was required, rather than the representation or rehearsal of verbal information. Our data are in line with these findings. Interestingly, in our study there are no differences between groups regarding the digit span backward, which is predominantly a measure of verbal working memory. Some studies have found impairments in this domain (D'Amico and Guarnera, 2005; Rosselli et al., 2006), whereas others suggest that children with DD do not appear to have a deficit in working memory for language-related tasks (McLean and Hitch, 1999; Schuchardt et al., 2008). Our results may be explained by the small group size of examined children and therefore additional research about the role of verbal working memory in children with DD is required.

In order to bring the findings from behavioral testing and functional MRI together we conducted correlation analyses on a whole brain level and based on functional ROIs. Whole brain analyses revealed no significant correlations, but significant results of our non-independent correlation analyses were found. These results have to be considered complementary to the results of the group contrast and interpreted carefully because of the small group size, which may contribute to the null result of the whole brain analysis, and significant ROI results, which were based a non- independent contrast between groups (Vul et al., 2009). Nevertheless, ROI analyses have the advantage compared to the whole brain analyses that they are based on independent voxel signals in unsmoothed data, which reduces the chance for a false positive result. Activation in the right IPS significantly correlated with the Corsi Block Tapping test and the digit span forward. Digit span forward is a measure of verbal short term memory and the correlation between the performance on this test and the IPS is in good accordance with a recent study (Majerus et al., 2008) showing a relation between activation of the right IPS and short term memory for order information. The correlation of the Corsi

Block tapping test performance and the IPS accentuates the close relationship between this region and the impaired spatial working memory capacity in children with DD. But as illustrated in Figure 2 there are also children without DD with bad performance at the Corsi Block tapping test showing decreased activation in the right IPS. The role of the IPS in calculation and in spatial working memory processes has been increasingly discussed in recent years and still remains a matter of debate (Ansari and Dhital, 2006; Cohen Kadosh et al., 2005; Dehaene et al., 1993; Dehaene et al., 2004; Dehaene et al., 1999; Fias and Fischer, 2005; Knops et al., 2006; Nieder, 2004, 2005; Shuman and Kanwisher, 2004; Zago et al., 2001). A study in adults investigated the contributions of spatial working memory manipulation during the addition of numbers (Zago et al., 2008). They found that calculation and spatial manipulation share a common network at the right fronto-parietal hemisphere and that the anterior IPS is involved in tasks requiring magnitude processing with symbolic (numbers) and nonsymbolic (locations) stimuli.

In our study we evaluated the neural underpinnings of spatial working memory in children with DD with a task similar to the Corsi Block Tapping test. Given that this task has no obvious arithmetical or numerical content, the differences in cortical activity between children with DD and normally achieving children in the right IPS strongly supports the notion that a spatial working memory deficit significantly contributes to DD. Our data support the view, that poor spatial working memory capacity may hinder the acquisition of spatial number representations in children with DD (Geary, 1993; von Aster and Shalev, 2007) . Therefore, our results provide novel information about the influence of spatial working memory on the acquisition of arithmetic competencies and help to further improve the understanding of DD.

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8. General Discussion

In this chapter, the key findings of the two studies will briefly be summarized, followed by a general discussion on results of the anatomical and functional underpinnings of DD investigated in this thesis.

The main goal of the present work was to investigate the anatomical and functional neural correlates of Developmental Dyscalculia from a 'domain general' perspective. For this purpose we investigated children with DD and control children by means of VBM and an fMRI experiment based on a spatial working memory task.

DD is a very heterogeneous disorder - a great variety of number specific and non-specific problems have to be considered as important factors, which contribute to arithmetic performance. This constitutes a serious problem in functional neuroimaging studies because one task is not able to address the whole spectrum of possible impairments. Contrary, VBM focuses on global structural differences independent of paradigm design or performance. Therefore, in the first study (**Study A**) entitled "Optimized Voxel Based Morphometry in Children with Developmental Dyscalculia" we investigated children with and without DD by using optimized VBM. We expected structural differences in parietal areas of children with DD in accordance to reported morphological and functional differences in the IPS of subjects with calculation disabilities. Furthermore, following a domain general approach, we assumed the entire neuronal network involved in number processing, including parietal, frontal, and cingulate areas to be altered in dyscalculic children.

Results show decreased grey matter volume in the right IPS compared to the control group, while the left IPS shows no differences in grey matter volume. Overall, findings about affected parietal hemispheres are inconsistent. The first study investigating volume differences in adolescents showed decreased grey matter at the left IPS (Isaacs et al., 2001), but examined children were born preterm. Several developmental studies indicate that brain activation during calculation changes with age (Ansari and Dhital, 2006; Rivera et al., 2005). There is evidence for increased functional specialization of the parietal cortex during development in mental arithmetic and magnitude judgment. Proficiency increase in these math operations is accompanied by decreased dependency on frontal areas and a reduced use of memory and attention resources (Ansari et al., 2005; Rivera et al., 2005). In other words, younger subjects require comparatively more working memory and attentional resources to achieve similar levels of mental arithmetic performance. Therefore, we assume that parietal regions of the investigated children in our study are not yet fully developed. Additionally, we found grey matter volume differences in our group at the bilateral middle frontal gyrus, the left inferior frontal gyrus and bilateral anterior cingulum. These findings support our hypotheses of a domain general impairment in DD and refer to an involvement of the attentional and the working memory system, which might have a negative effect on the acquisition of number representation and number processing capacities.

Based on the results of Study A and continuing our domain-general approach we investigated the role of spatial working memory processes in children with DD compared to normally-achieving children in the fMRI **Study B**, entitled "Dysfunctional Neural Network of Spatial Working Memory Contributes to Developmental Dyscalculia". The aim of this study was to evaluate how a domain-general factor, like spatial working memory contributes to DD. We found reduced activation in working memory relevant brain areas, such as the right IPS, the right inferior frontal lobe and in the right insula in children with DD as compared to the control group. Decreased activation in the right IPS of children with DD during a spatial working memory task may indicate that more domain general factors such as working memory influence the acquisition of arithmetic competencies and the development of a mental number line. Supplementary to these differences in neural activation clusters, analysis of the right IPS showed significant correlations with the Corsi Block Tapping test and the digit span forward. These results accentuate the close relationship between this region and the spatial working memory processes impaired in children with DD. In general, spatial manipulation and calculation share a common network at the right fronto-parietal hemisphere (Zago et al., 2008) – therefore, we conclude, that poor spatial working memory capacity in DD influences the formation of a core understanding of numerical information and the development of a 'mental number line'.

In calculation, working memory is used to retain, inhibit and order information into executable plans. When working memory is impaired, the amount of information increases and frequent errors rates lead to the storage of incorrect (inappropriate and often inconsistent) information. This impairs the development of stable long-term memory representations of number and arithmetic facts, which have an impact on the development of the mental number line.

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Curriculum Vitae

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Education and Qualification

2005-2008	University Children's Hospital Zurich, Switzerland MR-Center *Ph.D. project: Structural and Functional Brain Anatomy in Children with Developmental Dyscalculia: What Counts?*
1997-2005	University Zurich, Switzerland Institute of Psychology *Master of Science (Neuropsychology, Psychopathology, Social and Economic History)*
1993 - 1997	Gymnasium, Wettingen, Switzerland

Research Experience

07/2003 – 10/2003	Clinic for Epileptology, Bonn, Germany Supervisor: Prof. Dr. Helmstaedter *Internship*
02/2003 – 11/2004	University Zurich, Switzerland Department of Neuropsychology Supervisor: Prof. Dr. Jäncke *Internship / Research Assistant*

Postdoctoral Appointments

Since 08/2010	University Zurich, Switzerland Institute of Psychology Department of Neuropsychology *Research Assistant / Post-Doc*

Employment History

09/2008 – 12/2010	Children's Hospital, St.Gallen, Switzerland Department of Rehabilitation and Development *Neuropsychologist*

Peer Reviewed Publications

Rotzer, S., Loenneker, T., Kucian, K., Martin, E., Klaver, P.*, von Aster, M. 2009. Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. Neuropsychologia; 47(13):2859-65.
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Invited Talks

Rotzer, S. (2009, March). Brain functions and training intervention in children with developmental dyscalculia. EARLI Advanced Study Colloquium (ASC) 'Cognitive neuroscience meets mathematics education', Bruges, Belgium.

Rotzer, S. (2008, October). „Zahlensalat im Kopf – Hirnfunktionen bei Kindern mit Dyskalkulie". 16. Kongress des Bundesverbandes Legasthenie und Dyskalkulie e. V. "Chancengleichheit – Legasthenie und Dyskalkulie im Spannungsfeld zwischen Medizin, Bildung und Gesellschaft", Berlin, Germany.

Rotzer, S. (2007, September). Normale und gestörte Entwicklung des Rechnens: Ergebnisse der funktionellen MR-Bildgebung. SGPP – SGKJPP Jahreskongress, Bern, Switzerland.

Rotzer, S. (2007, September). "2 x 3 = 4": Neural Correlates in Children with Developmental Dyscalculia. 10th Congress of the Swiss Society of Psychology Differences, Diversitiy, and Change, Symposium "Neuropsychology of Developmental Disorders", Zurich, Switzerland.

Rotzer, S. (2007, May). Optimized voxel-based morphometry in dyscalculic and normally achieving children. European Society of Magnetic Resonance in Neuropediatrics, 9th Congress, Tübingen, Germany.

Rotzer, S. (2007, March). Optimierte voxel-basierte Morphometrie (oVBM) bei Kindern mit Dyskalkulie. Gemeinsame Jahrestagung der Deutschen Mathematiker-Vereinigung und der Gesellschaft für Didaktik der Mathematik, Berlin, Germany.

Posters/Abstracts

Rotzer, S., Kucian, K., Martin, E., von Aster, M., Loenneker, T. (2007, May). Optimized voxel-based morphometry in dyscalculic and normally achieving children. Poster presented at the Cognitive Neuroscience Society Annual Meeting (CNS), New York, NY.

Rotzer, S., Kucian, K., Martin, E., von Aster, M., Loenneker, T. (2007, September). Impact of Comorbidities on Subtypes of Developmental Dyscalculia. Poster presented at the ZNZ Symposium, Zurich.